Review

SOCS, inflammation and metabolism

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Abstract

Obesity is characterized by the development of low-grade chronic inflammation, which is a contributing factor in defective energy metabolism. A hallmark of metabolic dysregulation, obesity is a life-style disease that contributes to diabetes, hypertension, and dyslipidemia. Further, recent studies warn that obesity can be a risk factor for certain cancers and exacerbates infectious diseases. This association is called the "metabolic domino". Suppressor of cytokine signaling (SOCS) proteins are negative feedback regulators of cytokine and hormone signaling mediated by the JAK-STAT signaling pathway. SOCS proteins regulate cell-cell communication through JAK-STAT-dependent cytokines and signaling by Toll-like receptors (TLRs) and they may be influenced by dietary factors such as fatty acids and glucose. In this review, we focus on the role of the JAK-STAT-SOCS signaling cascade in metabolic disorder and obesity-related diseases.

Introduction

Human society has survived facing starvation, predation and infection. Advances in sciences including biology, medicine, agriculture, and engineering, have enriched lives. However, we now confront metabolic syndrome comprising disorders such as diabetes, cardiovascular disease, inflammation, and cancer. Obesity is the underlying cause of metabolic syndrome, which is a pandemic disease attributed to the changing global food system, wherein processed foods are heavily marketed, readily available, and affordable.

Because of their influence on metabolic syndrome, members of the suppressor of cytokine signaling (SOCS) family of proteins are the focus of intensive and numerous studies. Cytokine inducible SH2-protein (CIS)/SOCS proteins inhibit the activation of the JAK-STAT pathway and regulate signaling by interleukins (ILs), interferons (IFNs), members of the tumor necrosis factors (TNF) superfamily, growth factors, and hormones (Endo *et al.* 1997, Yoshimura *et al.* 2007). SOCS proteins regulate immune responses such as infection, inflammation and allergy, leukocyte homeostasis, and cell growth as well as metabolic processes such as glucose turnover (Howard & Flier 2006). Our literature search identified over 500 publications regarding the relationship between the SOCS family and metabolic syndrome (Figure 1, left). Among SOCS proteins, SOCS3 is potently involved in the progression of obesity and diabetes. These diseases are risk factor for cancers, infection, stroke, myocardial infraction, ulcers, infertility, and gallstones. Among a series of diseases, SOCS3 associates with obesity-related cancers (Figure 1, right). Recently, obesity has attracted great attention, because it is linked to the pathogenesis of certain cancers, including those of the colon, esophagus, breast, stomach, and pancreas (Wolin *et al.* 2010). Because patients with obesity-associated cancers experience higher mortality and are more resistant to chemotherapy, increased research efforts in this area are urgently required. In this review, our main focus is on the underlying mechanisms of metabolic dysregulation of the SOCS signaling pathway.

Structure and function of SOCS proteins

The genes that encode components of the JAK-STAT signaling pathway are transcriptionally regulated by its own SOCS family members (Inagaki-Ohara *et al.* 2013, Yasukawa *et al.* 2000). The structures of CIS/SOCS proteins are similar and include a central Src-homology 2 (SH2) domain that varies in length with limited homology in their N-terminal regions and a SOCS box motif in their C-terminal domains (Figure 2). The SOCS box interacts with Elongins B and C and

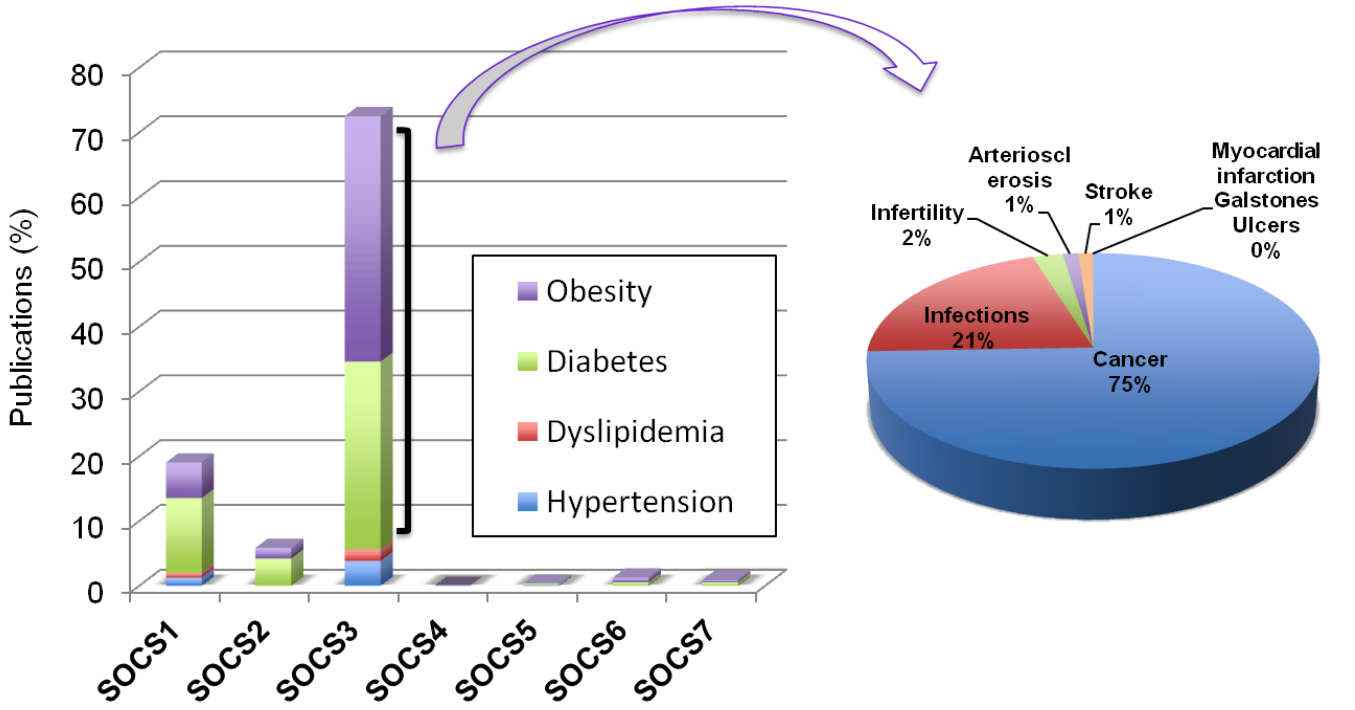

Figure 1. SOCS3 is a critical molecule in the development of metabolic syndrome and obesity-associated diseases. Each bar indicates the percentage of publications regarding metabolic syndrome on each SOCS family member according to a search of PubMed. 100 x (each SOCS)/(SOCS1-7) (left). Each pie chart shows the percentage of publications on obesity and diabetes-associated diseases involved in alteration of SOCS3 expression (right).

Cullin 5 to catalyze the ubiquitination of bound signaling protein, the RING-finger-domain-only protein RBX2 (which recruits E2 ubiquitin–transferase) (Figure 2) (Yoshimura *et al.* 2012). CIS/SOCS family proteins as well as other SOCS-box-containing molecules, likely act as E2 ubiquitin ligases. Because SOCS molecules bind to certain tyrosine-phosphorylated proteins, including Mal (toll-like receptor signaling) and IRS1/2 (insulin receptor substrate signaling) (Yoshimura *et al.* 2012), these targets may be ubiquitinated by SOCS. Unlike other SOCS proteins, SOCS1 and SOCS3 include a unique KIR domain, which is required for inhibition of JAK tyrosine kinase activity (Yasukawa *et al.* 1999) (Figure 2). The KIR domain of SOCS3 may function as a pseudosubstrate (Kershaw *et al.* 2013, Yasukawa *et al.* 1999) as well as a direct substrate of the ubiquitin-proteasome system (Piessevaux *et al.* 2008).

The role of SOCS proteins in leptin and insulin signaling

Obesity is characterized by chronic low-grade systemic and local inflammation. Infiltrating macrophages produce IL-1β and TNF-α, and T cells release IFN-γ as well as TNF-α. These pro-inflammatory cytokines are toxic for the pancreatic β-cells. Diabetes is caused when insulin production by β-cells is deficient (type 1 diabetes; T1D) or when cells that express the insulin receptor (IR) cannot respond to physiological concentrations of insulin (type 2 diabetes; T2D). Evidence indicates that genetic and environmental factors cause T1D (Bluestone *et al.* 2010). In contrast, T2D is caused by life-style (e.g. high-fat diet [HFD] and insufficient exercise) and accounts for more than 95% of patients with diabetes. T2D leads to alterations of glucose and lipid metabolism associated with insulin resistance (Lebrun & Van Obberghen 2008). Cytokines accelerate resistance to leptin and insulin in patients with T2D (Suchy *et al.* 2013). SOCS proteins regulate cytokine signaling and play important roles in pathophysiological processes leading to diabetes and obesity -associated diseases as well (Tanti *et al.* 2012).

Leptin Signaling

Leptin (product of ob gene), an adipocyte-derived hormone, binds to its receptor (ObR) in the hypothalamus to decrease food consumption and increase energy expenditure (Friedman & Halaas 1998). ObR is synthesized as multiple isoforms (ObRa–ObRf) as follows: four short isoforms with shortened intracellular tails (ObRa,c,d and f), one secreted (ObRe) and one long isoform (ObRb). Leptin belongs structurally to the long-chain helical cytokine family and activates the JAK-STAT signaling pathway and PI3K via ObRb, which is a type I cytokine receptor, similar to gp130

(Al-Qassab *et al.* 2009, La Cava & Matarese 2004). ObRb lacks intrinsic enzymatic activity and is activated by phosphorylation of its Cterminus by autophosphorylated JAK2, which is bound to the SH2 domain of STAT3 (Howard & Flier 2006). In the nucleus, STAT3 mediates gene transcription, including that of SOCS3. SOCS3 binds phosphorylated tyrosyl residue 985 (PY-985) of ObRb and to JAK2 to attenuate leptin receptor-mediated signaling. Phosphorylation of PY-985 of ObRb recruits the SH2 domain-containing protein-tyrosine phosphatase SHP-2 that functions upstream of extracellular-signal-regulated kinase (ERK) and c-fos transcription (Banks *et al.* 2000).

Leptin-stimulated signaling via STAT3 rapidly induces SOCS3, which inhibits signaling through the leptin receptor. Further studies of gene-targeted mice reveal that leptin's action specific to the central nervous system is sufficient to regulate body weight, food consumption, energy expenditure, glucose metabolism, and behavior (Gautron & Elmquist 2011). However, leptin's anorexigenic effects are suppressed in obese individuals and animals with HFD-induced obesity, despite elevated levels of serum leptin. This pathological condition is termed "leptin resistance" (Gautron & Elmquist 2011). These observations led to the proposal that SOCS3 is a potential mediator of leptin resistance. Further, peripheral administration of leptin to ob/ob mice specifically induces SOCS3 mRNA in regions of the hypothalamus that are important for regulating feeding behavior (Bjorbaek *et al.* 1998). Mice lacking SOCS3 from cells of the entire brain or only from proopiomelanocortin (POMC) neurons, which are leptin target neurons present in the arcuate nucleus of the hypothalamus, are resistant to HFD-induced obesity (Kievit *et al.* 2006, Mori *et al.* 2004). In addition, studies of SOCS3 transgenic mice show that overexpression of SOCS3 in POMC neuron but not in ObRb neurons is sufficient to impart leptin resistance and obesity mediated by antagonizing signaling through phosphorylated STAT3 and mTOR-S6K (Reed *et al.* 2010). In the periphery, leptin inhibits insulin secretion and expression of preproinsulin mRNA in the pancreatic β- cells. SOCS3 expressed by β-cells is involved in leptin-mediated inhibition of preproinsulin synthesis (Mori *et al.* 2007). Furthermore, leptin transactivates STAT3/STAT5b and the promoter of the preproinsulin 1 gene, and SOCS3 inhibits the activities of both promoters (Lebrun & Van Obberghen 2008), suggesting that SOCS3 inhibits directly the JAK-STAT signaling pathway as well as downstream signaling when the pathway is activated by leptin.

Insulin signaling

Insulin is secreted by the pancreas and stimulates the uptake of glucose and nutrients into peripheral target tissues. Like leptin, insulin reduces body weight and food intake, and regulates the expression of genes encoding neuropeptides as well as the activity of hypothalamic neurons. Similarly, signaling of the insulin receptor (IR) is mediated by phosphorylation of tyrosyl residues. Unlike ObRb, the IR has intrinsic tyrosine kinase activity that upon ligand binding, autophosphorylates the transmembrane domain of its β-subunit on tyrosyl residues Y1158, Y1162, and Y1163 to recruit downstream effector proteins, including IR substrates (IRS) 1 and 2. SOCS1 and SOCS3 bind to the IR. SOCS1 phosphorylated on its C-terminus (Y1158, Y1162 and Y1163), SOCS3, and protein-tyrosine phosphatase 1B (PTP-1B) suppress insulin and leptin signaling via different molecular mechanisms (Suchy *et al.* 2013) (Figure 3).

Increased expression of SOCS1 and SOCS3 induces insulin resistance in a variety models of obesity and diabetes via inhibition of JAK-STAT signal-

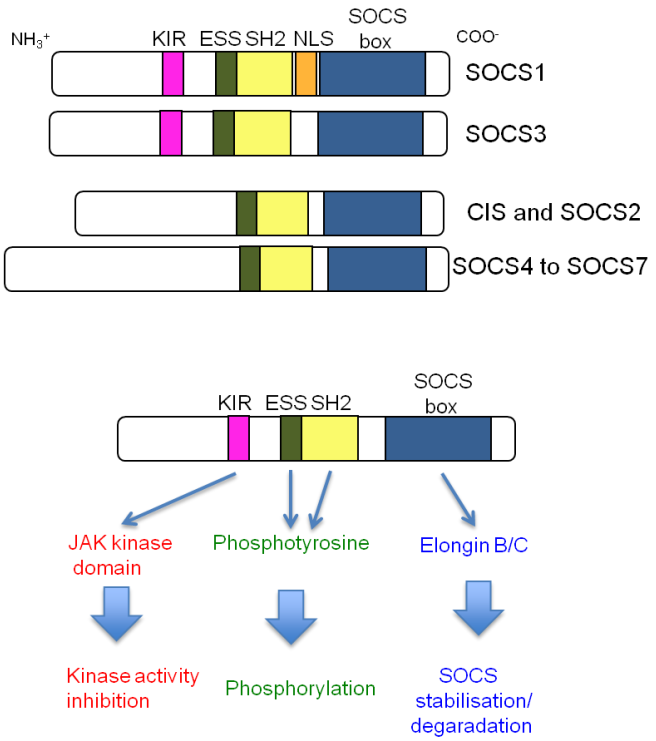

Figure 2. The structure and function of SOCS proteins. The SOCS family consists of eight members. All eight members share a central SH2 domain, extended SH2 domain (ESS), and a C-terminal SOCS box. In addition, SOCS1 and SOCS3 possess a kinase inhibitory region (KIR) that serves as a pseudo-substrate for JAKs that inhibits JAK function. Only SOCS1 contains a nuclear localization signal. A diagram of the extended interactions of SOCS with target proteins. The SOCS box interacts with several ubiquitinating machinery enzymes, i.e. Elongins B and C.

ing, competition for the binding of the IRS1 or targeting the degradation of IRS1 (Howard & Flier 2006, Yoshimura *et al.* 2007). However, SOCS1/RAG2-deficient mice, which survive to adulthood and gain body weight similar to wild-type mice, exhibit inflammation of adipose tissue, accompanied by elevated levels of leptin, TNF-α, and CD68 (a macrophage marker) in adipose tissue (Emanuelli *et al.* 2008). They also exhibit increased transcription of lipogenic genes in the liver, such as Srebp1c and Fas (Emanuelli *et al.* 2008). Furthermore, SOCS1 over-expression alone is insufficient to block total IFN-γ activity in pancreatic islets (Zaitseva *et al.* 2009). Interestingly, SOCS1-deficient neonatal mice exhibit drastic hypoglycemia and hypoinsulinemia, develop multiorgan inflammatory disease, and die before weaning (Jamieson *et al.* 2005). In contrast, SOCS3 haplo-deficient mice and mice with SOCS3-deficiency in the brain are resistant to HFD-induced obesity and are insulin resistance (Howard *et al.* 2004, Mori *et al.* 2004).

Inhibition of the expression of SOCS3 alone or together with SOCS1 and SOCS3, using antisense oli-

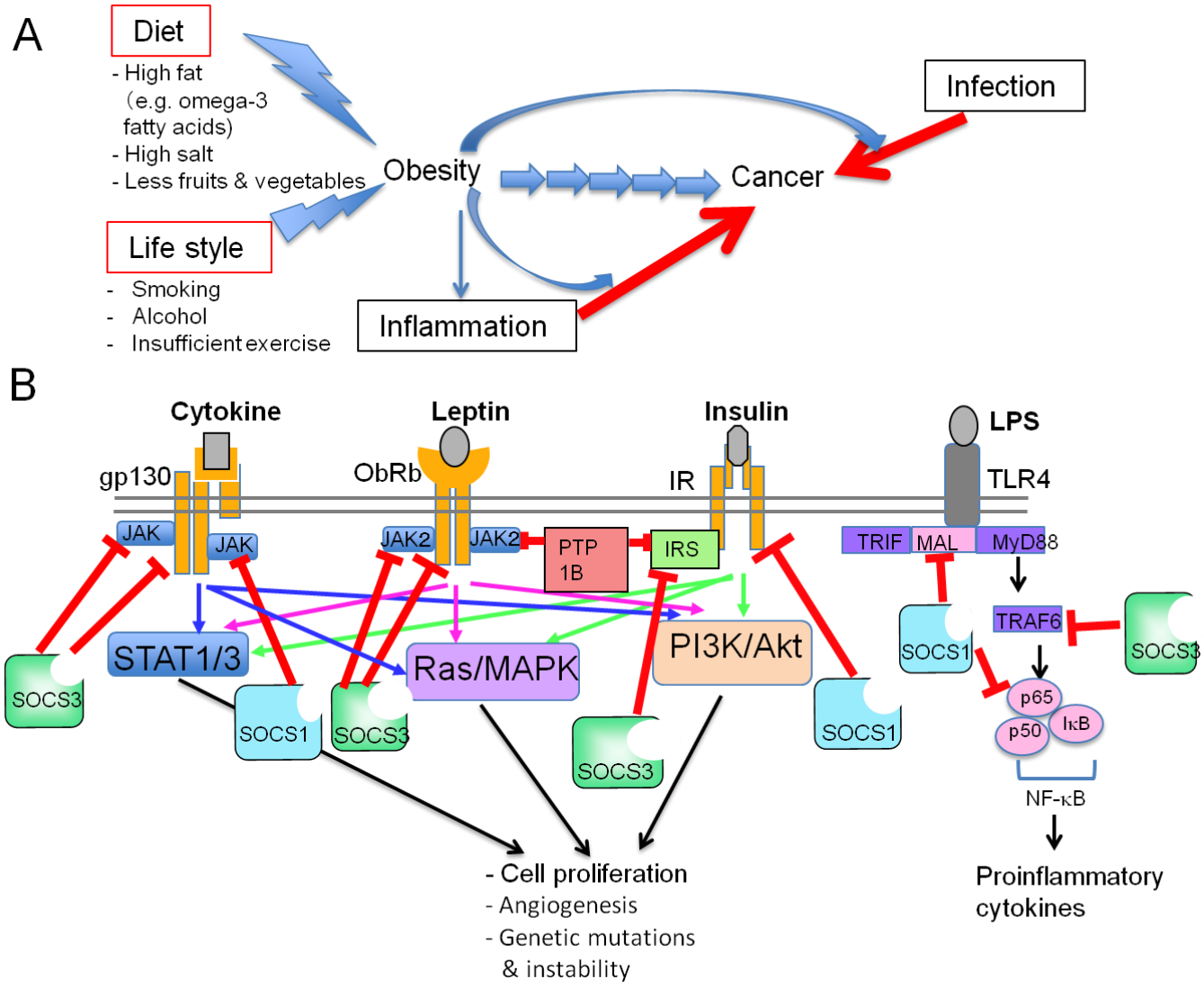

Figure 3. Multiple signaling pathways activated in obesity-associated diseases. A) Diet and lifestyle are critical factors for the development and regulation of obesity. Obesity is characterized by chronic low-grade systemic and local inflammation. Further, obesity accelerates inflammation- and infection-associated cancers through the receptors for cytokines, leptin, insulin, and bacterial components such as LPS via multiple signaling pathways including JAK-STAT, Ras-MAPK, PI3KAkt, and TLR. ObRb, which is analogous to gp130, lacks intrinsic kinase activity as illustrated in B). B) Binding of leptin to ObRb induces autophosphorylation and activation of noncovalently associated JAK2, which in turn, leads to phosphorylation of highly conserved tyrosyl residues in the intracellular domain of ObRb that recruit STAT3. STAT3 activation induces SOCS3 expression. Unlike gp130 and ObRb, IR possesses intrinsic tyrosine kinase activity that recruits and phosphorylates effector IRS molecules that, in turn, recruit adaptor molecules and mediate downstream signaling through PI3K and ERK. PTP1B inhibits leptin and insulin signaling by dephosphorylating JAK2 and IR, respectively.

gonucleotides in the livers of db/db mice, suppresses the expression of lipogenic genes (Ueki *et al.* 2004). Hepatic SOCS3 mediates insulin resistance; however, aged hepatocyte-specific SOCS3-deficient mice exhibit reduced insulin signaling in muscle, although insulin sensitivity in the liver is enhanced (Torisu *et al.* 2007). These studies suggest that lack of SOCS3 in the liver promotes systemic insulin resistance mediated by STAT3 activation induced by inflammatory factors produced from the liver. SOCS1-deficiency alone does not prevent HFD-induced obesity and insulin resistance. Considering the role of SOCS3 as a suppressor of IL-1β, IFN-γ, and TNF-α signaling in pancreatic β-cells, the SOCS3 pathway may prevent the onset of T2D as well as T1D (Bruun *et al.* 2009).

Several factors, such as IL-6, leptin, TNF-α, and infection with hepatitis C virus (HCV) regulate SOCS3 expression. For example, insulin increases the rate of SOCS3 expression in adipose tissue, liver, and muscle tissues (Emanuelli *et al.* 2001). Double deletions of the gene encoding SOCS3 and PTP-1B in the brain cells, compared with deleting them individually, improves sensitivity to insulin in an additive manner; however, the SOCS3 deletion contributes more significantly, which accounts for the low level of insulinemia detected in the double mutants (Briancon *et al.* 2010). This strategy is considered an important example of targeted therapy of T2D and obesity.

Function of SOCS proteins in Toll-like receptor (TLR) signaling

The SOCS proteins, in particular SOCS1 and SOCS3, inhibit TLR signaling as well as the JAK-STAT signaling pathway. Chronic inflammatory signaling is a key factor in the development of obesity, causes peripheral insulin, and accelerates leptin resistance. TLRs are a class of receptors that have key roles within the innate immune system by activating proinflammatory signaling cascades upon recognition of microbial and viral products (Medzhitov 2001). In particular, TLR4 contributes to the development of insulin resistance through its activation by an increased number of exogenous ligands, such as dietary fatty acids and lipopolysaccharide (LPS). Activation of the TLR4 signaling cascade induces the production of proinflammatory cytokines, chemokines, and reactive oxygen species (ROS), which are all effectors of innate immunity. TLR4 is expressed by many cells in insulin target tissues, including pancreatic β-cells as well as liver, skeletal muscle (Kim & Sears 2010). Therefore, TLR4 activation may suppress insulin action through proinflammatory cytokine signaling, ROS generation, and producing insulin-desensitizing factors.

The daily diet plays an important role in the development of obesity and diabetes, and the types and caloric content of meals are significant contributors to the inflammatory response. For example, consumption of foods high in carbohydrates and fat induce inflammation and increase in the LPS concentration in the plasma. Consumption of these foods, but not those with high-fiber content, elevates SOCS3 expression in circulating mononuclear cells (Ghanim *et al.* 2009). Long-chain polyunsaturated omega-3 fatty acids such as DHA and EPA antagonize TLR4 activation by saturated fatty acids and LPS (Lee *et al.* 2001, 2003, Shi *et al.* 2006). Consumption of sweets and cream increase the levels of TNF-α, IL-1β, and SOCS3 but not those of SOCS1 (Deopurkar *et al.* 2010). Further, cream enhances the post-meal spike in the concentration of circulating LPS concentration in contrast to drinking a beverage containing sugar. Moreover, SOCS3 signaling and NF-κB activation in circulating mononuclear cells are remarkably elevated when cream and soft drinks are consumed. These results suggest that the level of SOCS1 and SOCS3 induced by consuming certain kinds of food may differ, although SOCS proteins modulate insulin resistance.

Obesity-related diseases

Obesity-induced inflammation is an important contributor to the development of pathologies such as T2D, atherosclerosis, liver disease, infections, and some types of cancer (Gregor & Hotamisligil 2011, Wolin *et al.* 2010). In particular, cancer and infection are highly associated with the regulation of SOCS protein expression in obesity-associated diseases (Figure 1, right).

Cancer

Persistent inflammation increases cancer risk, which is driven by genetic alterations that cause inflammation and neoplasia. STATs and NF-κB are key coordinators of innate immunity and inflammation and are executors of tumor promoters (Inagaki-Ohara *et al.* 2013). Twenty percent of cancers can be attributed to obesity (Wolin *et al.* 2010), and increased cancer-related mortality (Reeves *et al.* 2007) attracts great attention as a global health problem. The number of people with diabetes has increased and is predicted to rise to 552 million by 2030 (Wild *et al.* 2004), suggesting that cancer risk will rise proportionately.

White adipose tissue (WAT) performs multiple functions other than to store lipids. The increase in the mass of WAT during the progression of obesity elevates the production of adipokines such as leptin, IL - 6, TNF-α, causing chronic mild inflammation. Dia-

betic patients are at significantly higher risk for common cancers including those of the breast, gastrointestinal (GI) (esophageal, colorectal) tract, liver, pancreas, urinary tract, and female reproductive tissues (Xu *et al.* 2014).

Breast cancer

Approximately 60% of breast cancers are hormone-dependent. The hormonal changes that occur postmenopause are attributed to a specific metabolic state that represents a greater risk for breast cancer. These changes are considered indispensable for a more effective therapy (Maccio & Madeddu 2011). Among adipokines, leptin is the most intensively studied regarding its metabolism and role in obesityrelated carcinogenesis, because leptin induces physiological responses in peripheral tissues other than those involved in neuronal activity. Increased expression of leptin and ObRb in human grade-III invasive breast tumors is associated with shorter time to tumor recurrence and mortality (Garofalo *et al.* 2006, Maccio *et al.* 2010).

Tumor cells derived from MMTV-Wnt1 mice, a widely used model of mammary tumors, show decreased growth in ob/ob mice (leptin-deficient) compared with diet-induced obese mice with an intact leptin signaling pathway (Zheng *et al.* 2011). This result suggests that leptin signaling plays an essential role in the growth and survival of tumors induced by MMTV-Wnt1. Tumor initiating stem cells express high levels of ObR to promote tumorigenesis caused by STAT3 activation and by inducing pluripotencyassociated transcription factors such as Oct4 and Sox2 (Feldman *et al.* 2012). In patients with obesity-related breast cancer, the JAK2-STAT3 pathway is activated and SOCS3 is down-regulated (Santillan-Benitez *et al.* 2014). These effects of leptin are mediated through a set of responses of ObRb-positive tumor cells, including a cancer stem cell population that expresses the ObRb. These findings suggest that leptin affects tumor initiation and progression through STAT3 activation.

Gastrointestinal (GI) cancer

The relative risk of GI cancer in obese individuals is highly prevalent among patients with obesityassociated Barrett's esophagus and colon cancer (Wolin *et al.* 2010). The combination of adenomatous polyposis coli (Apc) and db/db mice enhances Apc-driven tumorigenesis of the small intestine and induces gastric and colonic tumors. In contrast, db/db mice do not develop GI neoplasia (Gravaghi *et al.* 2008). Recently, gastric cancer has emerged as an obesity-associated cancer. Normal stomach tissues spontaneously express leptin and ObRb, and their expression levels increase during carcinogenesis (Bado *et al.* 1998, Inagaki-Ohara *et al.* 2014), and induce autocrine signaling (Hoda *et al.* 2007), suggesting that the stomach is more susceptible to ObR signaling than other tissues. Approximately 90% of gastric cancers are gastric adenocarcinomas (GCA), which are further categorized as distal or non-cardia GCA and proximal or cardia GCA. Interestingly, cardia GCA is associated with obesity (Cho *et al.* 2012, O'Doherty *et al.* 2012), suggesting that the unique localization of the leptin-ObR signaling pathway to cells of the GI tract functions predominantly in the early phase of human GC and serves as a biomarker. Therefore, targeting this pathway may be invaluable for treatment.

Hepatic cancer

Leptin's oncogenic role, including its capability to enhance tumor invasiveness and migration of hepatocellular carcinoma (HCC) cells, may be antagonized by adiponectin in HCC through suppression of STAT3 and Akt phosphorylation when SOCS3 is up-regulated (Sharma *et al.* 2010). Studies conducted in vitro reveal that the SOCS3 binding site is essential for the interaction with IRS1 and IRS2, whereas the affinity of SOCS1 for a domain within the catalytic loop is crucial for IRS2 (Ueki *et al.* 2004). SOCS1 and SOCS3 bind to the IR in cells, and their overexpression impairs the phosphorylation of IRS1 and IRS2 stimulated by insulin. Insulin resistance is caused by IL-6 due to suppression of tyrosine phosphorylation of IRS-1 through the induction of SOCS3 in murine primary hepatocytes and human hepatocarcinoma cells (Wunderlich *et al.* 2013). Indeed, IL-6-deficient mice are resistant to diethylnitrosamine (DEN)-induced carcinogenesis when fed a HFD (Park *et al.* 2010). Recently, Shimizu *et al.* (2011) showed that several signaling pathways including insulin/IGF-1/PI3K/Akt, ERK, JNK, and STAT3 are important in DEN-induced liver carcinogenesis in db/db mice. SOCS3 expression is reduced in the levers of HCC patients, which is supported by findings that mice with hepatocyte-specific deletion of SOCS3 are resistant to concanavalin A-induced hepatocarcinogenesis (Ogata *et al.* 2006).

Collectively, these studies reveal that leptin exerts its actions centrally and provides beneficial effects to peripheral organs. However, although such peripheral functions of leptin exist, chronic JAK-STAT3- SOCS3 pathway activity in obesity is mainly derived from other signals that, in contrast, act in the periphery as well as the CNS. Further, crosstalk between leptin and IGF-1 significantly increases the proliferation as well as invasion and migration of breast cancer cells, suggesting that the cooperation of several signaling pathways is required to induce obesity-associated carcinogenesis.

Infection

Hepatitis C virus

Overwhelming epidemiological evidence indicates that persistent infection with HCV and HBV is a major risk factor for the development of HCC (Koike *et al.* 2008). In transgenic mice carrying the gene encoding the HCV core protein (PA28 gamma (+/+) Core Tg), the HCV core protein induces hyperexpression of TNF-α (Miyamoto *et al.* 2007), and HCV infection causes insulin resistance and T2D, which is sufficient to impair insulin signaling in vitro through the SOCS protein activation and the consequent decrease in IRS- 1 expression (Pascarella *et al.* 2011).

Chronic HCV infection of humans is treated with a combination of Peginterferon (a long acting IFN) and Ribavirin (guanosine analog that inhibits RNA synthesis). These drugs contribute to decreased sensitivity to interferon, which is inhibited by SOCS3 (del Campo *et al.* 2010). Interestingly, SOCS1-deficient mice show hyperglycemia but die before reaching three weeks of age due to enhanced IFN-γ signaling (Starr *et al.* 1998). Human embryonic stem cell-derived hepatocytes (hESC-Heps) are capable of supporting the full HCV life cycle and viral infection to a lesser extent compared with the HUh 7 hepatocarcinoma cell line that produces IL-29, a type III IFN, upon stimulation by HCV infection (Zhou *et al.* 2014). Considering that the level of viral infection and replication in hESC-Heps is increased by addition of JAK inhibitor I that modulates signaling through the JAK-STAT pathway as well as the downstream response to IFN, "tunable" hESC-Heps may serve as a platform for the development of anti- HCV drugs.

Influenza

The association between obesity and influenza was first reported during the 2009 influenza A (H1N1) pandemic (Louie *et al.* 2011, Morgan *et al.* 2010). Obese volunteers infected with influenza A (H1N1) show a reduced ability to produce type I IFN in response to the TLR3 ligand, delayed proinflammatory responses, and increased basal expression of SOCS3 but not SOCS1 (Teran-Cabanillas *et al.* 2014). Dietinduced obese mice exhibit similar responses. In these mice, the number of influenza virus-specific CD8+- memory T cells in the lung, an important cell population for protection against the subsequent virus exposure is decreased, but expression of SOCS1 and SOCS3 is increased (Karlsson *et al.* 2010). These results suggest that new vaccine strategies are required for obese individuals, because the standard vaccine that induces the proliferation of memory T cells may be less effective in an obese population.

Intestinal microbiota

It is important to understand that the output of signaling pathways that are activated by certain bacteria may protect against intestinal inflammation or obesity. Members of the phyla Bacteroidetes and Firmicutes dominate the gut microbiome, and an increased ratio of Firmicutes to Bacteroidetes is implicated in the development of adult obesity (Eckburg *et al.* 2005, Ley *et al.* 2006, Turnbaugh *et al.* 2006). Obesity is characterized by chronic low-grade inflammation with reduced GI barrier function involving a variety factors and inflammatory mediators (Chakraborty *et al.* 2010). "Metabolic endotoxemia" can initiate obesity and insulin resistance through gastrointestinal bacteria- triggered SOCS3 signaling. High-fat and high-fructose diets alter the composition of the gut microbiota and the permeability of the gut, which increase the proliferation of enterobacterial species and the levels of circulating LPS (Cani & Delzenne 2009, Kim & Sears 2010). Germ-free mice or mice treated with antibiotics specific for gram-negative bacteria do not exhibit HFD -induced insulin resistance or other metabolic abnormalities associated with obesity (Backhed *et al.* 2007, Cani *et al.* 2008). The presence of body fat-inducing gut microbiota may be associated with hypothalamic signs of SOCS3-mediated leptin resistance (Schele *et al.* 2013). Further, the strong correlation between increased LPS concentrations and HFD-induced endotoxemia, an important component of obesity-associated inflammation in obese patients, is consistent with enhanced expression of TLR4 and NF-κB in circulating mononuclear cells (Cani *et al.* 2008, Ghanim *et al.* 2009). Deletion of Tlr4 from the myeloid cells protects mice against HFD-induced inflammation, adipose macrophage infiltration, and insulin resistance (Saberi *et al.* 2009). TLR5 binds to bacterial flagellin, and mice lacking this receptor display hyperphagia and develop the characteristic features of metabolic syndrome, including hyperlipidemia and insulin resistance (Vijay-Kumar *et al.* 2010). These metabolic changes correlate with changes in the composition of the gut microbiota, and transfer of the gut microbiota from TLR5-deficient mice to wild-type germ-free mice confers many features of metabolic syndrome to the latter.

Emerging evidence suggest that the GI tract is the origin of inflammation in HFD-induced obesity as well as adipose tissue. A HFD promotes inflammation in the GI tract, which is considered a potential source of inflammation associated with HFD-induced obesity. Adult germ-free (GF) mice have less body fat and do not become obese when they are fed a HFD, and replacing the microbiota of adult GF mice with the microbiota harvested from conventional mice increases in body fat (Backhed *et al.* 2004, Backhed *et al.* 2007).

These results indicate that nonpathogenic enteric bacteria in healthy individuals may play a key role in diet-induced obesity.

Mice devoid of PTP1B are resistant to diet-induced obesity (Bence *et al.* 2006, Elchebly *et al.* 1999, Owen *et al.* 2012). Furthermore, knockdown of PTP1B expression in the RAW264.7 macrophage cell line increases the production of IL-6, TNF-α, and IFN-β in response to a variety of TLR ligands, indicating that PTP1B can act as a negative regulator of TLR4-signaling in macrophages (Xu *et al.* 2008). Myeloid cell-specific PTP1B knockout (LysM-PTP1B) mice resist LPS-induced endotoxemia and hepatic damage associated with decreased TNF-α expression and show an increase in basal and LPS-induced IL-10 production associated with enhanced STAT3 activation (Grant *et al.* 2014). These findings suggest that myeloid PTP1B is a previously unrecognized inhibitor of STAT3/IL-10 mediated signaling and may serve as a target for treating inflammation and diabetes in obese patients.

Concluding remarks

Over the past decade, SOCS proteins have been clearly shown to inhibit the leptin and insulin signaling pathways in vitro and in vivo and to influence energy balance and glucose homeostasis. These discoveries highlight the importance of SOCS for regulating the mechanisms of onset and development of diseases involved in metabolic dysfunction in central and peripheral tissues through the JAK-STAT signaling cascade as well as through crosstalk with other mediators (Figure 3). In the future, SOCS proteins will likely provide therapeutic targets for T2D and obesity-associated cancer, although investigations should take into account the induction of SOCS proteins by diverse cytokines and cell types.

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Author Contributions

K. I-O. wrote the manuscript and A. Y. provided comments.

Conflicts of Interest

The authors declare no conflicts of interest.

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